

APPENDIX B

LISTING OF THE CLAIMS
FOR U.S. APPLICATION NO. 10/477,802

(Underlined represents insertions; double brackets or strike-through represents deletions)

1.-45. (Canceled)

46. (Currently amended) A method of inhibiting Flt4 receptor tyrosine kinase (Flt4) function in a mammalian organism with a neoplastic disease, comprising administering to said mammalian organism a composition,

wherein said neoplastic disease is a breast carcinoma characterized by expression of Flt4 in vascular endothelial cells,

wherein said composition comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vascular endothelial cells of said organism, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen, selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2,

wherein the composition is administered to the organism in an amount effective to inhibit Flt4 function in the organism.

47. (Canceled)

48. (Previously presented) A method according to claim 46 wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said bispecific antibody or fragment thereof.

49-61. (Canceled)

62. (Currently amended) A method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising administering to said mammal a composition, said composition

comprising an inhibitor of binding between Flt4 ligand protein and Flt4 expressed in cells of said mammal, thereby inhibiting Flt4 function, where the inhibition of Flt4 function treats breast cancer,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

63. (Previously presented) A method according to claim 62 wherein said mammal is human.

64. (Previously presented) A method according to claim 62 comprising a screening step preceding the administering step, wherein the screening step comprises screening a human to identify breast cancer characterized by blood vessel endothelial cells expressing Flt4; and

wherein the administering step comprises administering the composition to a human identified by the screening step as having breast cancer characterized by blood vessel endothelial cells expressing Flt4.

65-66. (Canceled)

67. (Currently amended) A method for treating a neoplastic disorder in a human subject, comprising:

(a) screening a human subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and

(b) administering a composition to a human subject identified according to (a) as having a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4, to inhibit Flt4 mediated proliferation of said Flt4-expressing cells, where inhibition of said proliferation treats the neoplastic disorder,

wherein the composition comprises a means for inhibiting Flt4 function in mixture with a pharmaceutically acceptable diluent, adjuvant, or carrier, wherein the means for inhibiting comprises a member selected from the group consisting of:

([[a]] i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody;

([[b]] ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;

([[c]] iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody;

([[d]] iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

([[e]] v) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

68. (Currently amended) ~~A method according to claim 67~~ A method for treating a neoplastic disorder in a human subject, comprising:

(a) screening a human subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and

(b) administering a composition to a human subject identified according to (a) as having a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4, to inhibit Flt4 mediated proliferation of said Flt4-expressing cells, where inhibition of said proliferation treats the neoplastic disorder,

wherein the composition comprises a means for inhibiting Flt4 function in mixture with a pharmaceutically acceptable diluent, adjuvant, or carrier, wherein the

means for inhibiting comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

69. (Previously presented) A method according to claim 68 wherein said blood vascular endothelial marker antigen is selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2.

70. (Previously presented) A method according to claim 68 wherein the means for inhibiting further comprises an anti-neoplastic agent conjugated to said bispecific antibody or fragment thereof.

71. (Canceled)

72. (Previously presented) A method of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells, comprising administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vessel endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the blood vessel endothelial cells,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

73. (Previously presented) A method of inhibiting proliferation of endothelial cells in a human organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in endothelial cells, comprising administering to said human organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

74. (Previously presented) A method according to claim 72 or 73, wherein said blood vascular endothelial marker antigen is selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2.

75. (Previously presented) A method according to claim 72 or 73, wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said bispecific antibody or fragment thereof.

76. (Canceled)

77. (Currently amended) A method ~~according to claim 72, wherein the disease is~~ of inhibiting proliferation of blood vessel endothelial cells in a mammalian organism having a breast carcinoma characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessel endothelial cells ~~in vascular endothelial cells, comprising administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in blood vessel endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the blood vessel endothelial cells,~~

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

78. (Previously presented) A method of inhibiting proliferation of endothelial cells in a human organism having a breast carcinoma characterized by expression of Flt4 tyrosine kinase (Flt4) in vascular endothelial cells, comprising administering to said human organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in endothelial cells of said organism, thereby inhibiting Flt4-mediated proliferation of the cells, wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

79. (Previously presented) A method according to claim 78 wherein said blood vascular endothelial marker antigen is selected from the group consisting of PAL-E, VEGFR-1, and VEGFR-2.

80. (Previously presented) A method according to claim 78 wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said bispecific antibody or fragment thereof.

81. (Currently amended) A method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessels, comprising administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting in an amount effective to inhibit Flt4-mediated proliferation of ~~the cells~~ said blood vessels in the organism, wherein said inhibitor comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

82. (Currently amended) A method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessels, comprising administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting in an amount effective to inhibit Flt4-mediated proliferation of ~~the cells~~ said blood vessels in the organism,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

83. (Previously presented) A method according to claim 81 or 82 wherein said organism is human.

84. (Previously presented) A method according to claim 83, wherein the human has a tumor characterized by blood vessels that express Flt4.

85. (Previously presented) A method of inhibiting the growth or the metastatic spread of a tumor in a mammalian organism, comprising administering to a mammalian organism a composition that comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 receptor tyrosine kinase (Flt4) expressed in cells of said organism, wherein the mammalian organism has a tumor characterized by blood and lymphatic vessels that express Flt4, and wherein the composition inhibits proliferation of the blood and lymphatic vessels, thereby inhibiting growth or metastatic spread of the tumor, wherein the inhibitor comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

86. (Previously presented) A method of inhibiting the growth or the metastatic spread of a tumor in a mammalian organism, comprising administering to a mammalian organism a composition that comprises an inhibitor of the binding of an Flt4 ligand protein to Flt4 receptor tyrosine kinase (Flt4) expressed in cells of said organism, wherein the mammalian organism has a tumor characterized by blood and lymphatic vessels that express Flt4, and wherein the composition inhibits proliferation of the blood and lymphatic vessels, thereby inhibiting growth or metastatic spread of the tumor,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

87. (Currently amended) A method according to claim 85 or 86, comprising a diagnosing step prior to the administering step, said diagnosing step comprising identifying a mammalian organism that is a human patient having a tumor characterized by blood vessels that express Flt4.

88. (Currently amended) A method according to claim ~~87~~ 85 ~~or 86~~, comprising a diagnosing step prior to the administering step, said diagnosing step comprising identifying a mammalian organism that is a human patient having lymph node metastasis of a tumor, wherein the lymph node comprises cells expressing Flt4.

89. (Currently amended) A method of inhibiting neoplastic cell growth in a human subject, comprising:

(a) screening a human subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and

(b) administering a composition to a human subject identified according to (a) as having a neoplastic disorder characterized by blood vessels that comprise endothelial cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, ~~thereby inhibiting in an amount effective to inhibit~~ Flt4-mediated proliferation of said Flt4-expressing cells and inhibit neoplastic cell growth in the subject, wherein the inhibitor comprises a member selected from the group consisting of:

(i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody;

(ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;

(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody;

(iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(v) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

90. (Currently amended) A method of inhibiting neoplastic cell growth in a human subject, comprising:

(a) screening a human subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4); and

(b) administering a composition to a human subject identified according to (a) as having a neoplastic disorder characterized by blood vessels that comprise endothelial cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, ~~thereby inhibiting in an~~ amount effective to inhibit Flt4-mediated proliferation of said Flt4-expressing cells and inhibit neoplastic cell growth in the subject,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

91. (Currently amended) A method of inhibiting neoplastic cell growth in a mammalian subject, comprising:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4), wherein the screening comprises

(i) contacting tissue from the mammalian subject with a composition comprising an antibody or antibody fragment that specifically binds Flt4;

(ii) detecting said antibody or antibody fragment bound to cells in said tissue; and

(iii) screening for a neoplastic disorder from the quantity or distribution of said antibody or antibody fragment bound to cells in said tissue, wherein the detection of said antibody or antibody fragment bound to blood vessel endothelial cells is correlated with the presence of a neoplastic disease; and

(b) administering a composition to a mammalian subject identified according to (a) as having a neoplastic disorder characterized by blood vessel endothelial

cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells and inhibiting neoplastic cell growth in the subject, wherein the inhibitor comprises a member selected from the group consisting of:

(i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody

(ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;

(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody;

(iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(v) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

92. (Currently amended) A method of inhibiting neoplastic cell growth in a mammalian subject, comprising:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4), wherein the screening comprises

(i) contacting tissue from the mammalian subject with a composition comprising an antibody or antibody fragment that specifically binds Flt4;

(ii) detecting said antibody or antibody fragment bound to cells in said tissue; and

(iii) screening for a neoplastic disorder from the quantity or distribution of said antibody or antibody fragment bound to cells in said tissue, wherein the detection of said antibody or antibody fragment bound to blood vessel endothelial cells is correlated with the presence of a neoplastic disease; and

(b) administering a composition to a mammalian subject identified according to (a) as having a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells and inhibiting neoplastic cell growth in the subject,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

93. (Previously presented) A method according to claim 91 or 92, wherein said tissue comprises mammary tissue.

94. (Currently amended) A method of inhibiting genesis of blood vessels in a mammalian organism having a disease characterized by expression of Flt4 tyrosine kinase (Flt4) in blood vessels, comprising administering to said mammalian organism a composition, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4-mediated proliferation of ~~the cells~~ blood vessels in the organism that express Flt4, wherein said inhibitor comprises a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21).

95. (Previously presented) A method according to claim 94 wherein said organism is human.

96. (Previously presented) A method according to claim 95, wherein the human has a tumor characterized by blood vessels that express Flt4.

97. (Currently amended) The method of any one of claims ~~53, 61~~, 67, 81, 85, 89 and 91, wherein the inhibitor is an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody.

98. (Currently amended) The method of any one of claims ~~53, 61~~, 67, 81, 85, 89 and 91, wherein the inhibitor is a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21).

99. (New) A method for antagonizing the function of Flt4 receptor tyrosine kinase (Flt4) in a mammalian organism, comprising administering to the organism a composition comprising a bispecific antibody, or fragment thereof, in an amount effective to antagonize the function of Flt4 in the mammal,

wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen; and

wherein said organism has a neoplastic disorder characterized by blood vessels comprising endothelial cells that express Flt4.

100. (New) The method according to claim 99, wherein the organism is human.

101. (New) The method according to claim 99, wherein said composition further comprises an anti-neoplastic agent conjugated to said antibody or antibody fragment.

102. (New) A method of inhibiting neoplastic cell growth in a mammalian subject, comprising:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4; and

(b) administering a composition to a mammalian subject identified according to (a) as having a neoplastic disorder characterized by cells expressing Flt4,

said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, where the composition is administered in an amount effective to inhibit Flt4-mediated proliferation of said Flt4-expressing cells and inhibit neoplastic cell growth in the mammal, wherein said inhibitor comprises a polypeptide selected from the group consisting of:

(i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody;

(ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;

(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody

(iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(v) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

103. (New) A method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising administering to said mammal a composition, said composition comprising an inhibitor of binding of an Flt4 ligand protein to Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function and treating the mammal, wherein the inhibitor comprises a member selected from the group consisting of:

(a) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody;

(b) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;

(c) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody;

(d) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(e) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

104. (New) A method of treating a mammal having breast cancer characterized by blood vessel endothelial cells that express Flt4 tyrosine kinase (Flt4), comprising administering to said mammal a composition, said composition comprising an inhibitor of binding between Flt4 ligand protein and Flt4 expressed in cells of said organism, thereby inhibiting Flt4 function and treating the mammal,

wherein the inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen.

105. (New) The method according to claim 104 or 105, wherein said mammal is human.

106. (New) The method according to claim 105, comprising a screening step preceding the administering step, wherein the screening step comprises screening a human to identify breast cancer characterized by blood vessel endothelial cells expressing Flt4; and

wherein the administering step comprises administering the composition to a human identified by the screening step as having breast cancer characterized by blood vessel endothelial cells expressing Flt4.

107. (New) A method of inhibiting neoplastic cell growth in a mammalian subject, comprising:

(a) screening a mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4; and

(b) administering a composition to a mammalian subject identified according to (a) as having a neoplastic disorder characterized by cells expressing Flt4, said composition comprising an inhibitor of the binding of an Flt4 ligand protein to Flt4 expressed in cells of said subject, thereby inhibiting Flt4-mediated proliferation of said Flt4-expressing cells and inhibiting neoplastic cell growth,

wherein said inhibitor comprises a bispecific antibody, or fragment thereof, wherein said antibody or fragment specifically binds Flt4 and specifically binds a blood vascular endothelial marker antigen selected from the group consisting of PAL-E, VEGFR-1 and VEGFR-2.

108. (New) The method according to claim 107, wherein the mammalian subject is human.

109. (New) The method according to claim 107, wherein said inhibitor further comprises an anti-neoplastic agent conjugated to said bispecific antibody.

110. (New) The method according to claim 107 wherein the screening comprises:

(a) contacting tissue from the mammalian subject with a composition comprising an antibody or antibody fragment that specifically binds Flt4;

(b) detecting said antibody or antibody fragment bound to cells in said tissue; and

(c) screening for a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4 from the quantity or distribution of said antibody bound to cells in said tissue.

111. (New) The method according to claim 110, wherein in said screening, the detection of said antibody or antibody fragment bound to blood vessel endothelial cells is correlated with the presence of a neoplastic disease.

112. (New) The method according to claim 110 wherein said tissue comprises mammary tissue.

113. (New) A method of treating a human subject comprising:

(a) screening a human subject to identify tumor blood vasculature that expresses Flt4 tyrosine kinase (Flt4), and

(b) administering to a subject identified by such screening as having tumor blood vasculature that expresses Flt4 a composition that comprises an inhibitor of binding between an Flt4 ligand and Flt4, in an amount effective to inhibit Flt4-mediated proliferation of said blood vasculature in the subject,

wherein said inhibitor comprises a member selected from the group consisting of:

(i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody;

(ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody;

(iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody;

(iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and

(v) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent.

114. (New) A method of treating a human subject comprising:

(a) administering to a subject that has a neoplastic disease characterized by expression of Flt4 tyrosine kinase (Flt4) in vascular endothelial cells a composition that comprises an inhibitor of binding between an Flt4 ligand and Flt4, in an amount effective to inhibit Flt4-mediated proliferation of said blood vasculature in the subject,

wherein said inhibitor comprises a member selected from the group consisting of: (i) an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody; (ii) an anti-VEGF-C antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-C antibody; (iii) an anti-VEGF-D antibody or a polypeptide comprising an antigen binding fragment of said anti-VEGF-D antibody; (iv) a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21); and (v) a polypeptide comprising an Flt4 binding fragment of human prepro-VEGF-C (SEQ ID NO: 21) or human prepro-VEGF-D (SEQ ID NO: 22) conjugated to an antineoplastic agent; and

(b) monitoring the progression of the therapy, said monitoring including measuring the quantity or distribution of Flt4 within blood vasculature of the human subject.

115. (New) The method of claim 114, wherein the monitoring comprises exposing a cell sample from the human subject to an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody, and measuring Flt4 by detecting binding of said antibody or polypeptide to Flt4 in the cell sample.

116. (New) The method of claim 67, wherein the screening of the human subject to identify a neoplastic disorder characterized by blood vessel endothelial cells expressing Flt4 receptor tyrosine kinase (Flt4) comprises contacting cells from the

subject with a Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody, and detecting blood vessel endothelial cells stained with said antibody or polypeptide.

117. (New) The method of claim 81, further comprising monitoring the progression of the inhibiting, said monitoring including measuring the quantity or distribution of Flt4 within blood vasculature of the human subject.

118. (New) The method of claim 87, wherein the identifying comprises contacting cells from a human with a Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody, and detecting blood vessel endothelial cells stained with said antibody or polypeptide, thereby diagnosing the human as having a tumor characterized by blood vessels that express Flt4.

119. (New) The method of claim 91, wherein the mammalian subject is human.

120. (New) The method of claim 97, wherein the anti-Flt4 antibody is a human or humanized antibody.

121. (New) The method of claim 102, wherein the screening of the mammalian subject to identify a neoplastic disorder characterized by blood vessels that comprise endothelial cells that express Flt4 comprises contacting cells from the organism with an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody, and detecting blood vessel endothelial cells stained with said antibody or polypeptide.

122. (New) The method of any one of claims 102, 103, 113, and 114, wherein the inhibitor is an anti-Flt4 antibody or a polypeptide comprising an antigen binding fragment of said anti-Flt4 antibody.

123. (New) The method of claim 122, wherein the anti-Flt4 antibody is a human or humanized antibody.

124. (New) The method of any one of claims 102, 103, 113, and 114, wherein the inhibitor is a soluble polypeptide comprising a fragment of Flt4, wherein the polypeptide and the fragment are capable of binding to human VEGF-C (SEQ ID NO: 21).

125. (New) The method of any one of claims 67, 81, 85, 86, 89, 91, 102, 103, 113, and 114, wherein the inhibitor further comprises an anti-neoplastic agent conjugated thereto.

126. (New) The method of any one of claims 67, 81, 85, 86, 91, 102, 103, 113, and 114, wherein the composition further comprises a pharmaceutically acceptable diluent, adjuvant, or carrier.